U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication

FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease

Safety Announcement

[08-28-2019] The Food and Drug Administration (FDA) has received reports that the use of Mavyret, Zepatier, or Vosevi to treat chronic hepatitis C in patients with moderate to severe liver impairment has resulted in rare cases of worsening liver function or liver failure. All these medicines contain a hepatitis C virus (HCV) protease inhibitor and are not indicated for use in patients with moderate to severe liver impairment. In most patients, symptoms resolved or new onset worsening of liver function improved after stopping the medicine. These medicines have been widely used and are safe and effective in patients with no or mild liver impairment.

In many of the reported cases, liver failure occurred in patients who had signs and symptoms of moderate to severe liver impairment (Child-Pugh B or C) or other serious liver problems and should not have been treated with these medicines. In some cases, patients were reported to have no cirrhosis or compensated cirrhosis with mild liver impairment (Child-Pugh A) despite having evidence of decreased platelets at baseline or an increase in the pressure within the portal vein that carries blood from the digestive organs to the liver. In addition, some cases had other significant pre-existing risk factors such as liver cancer, alcohol abuse, or serious medical illnesses associated with serious liver problems. These factors may have contributed to clinical worsening of liver function or liver failure during treatment with these hepatitis C medicines. In most cases, liver failure or decompensation typically occurred within the first 4 weeks of starting treatment. We will continue to monitor this safety concern and will communicate any new information to the public if it becomes available.

Mavyret, Zepatier, and Vosevi are FDA-approved to treat chronic hepatitis C in patients without liver impairment or with mild liver impairment (Child-Pugh A). Clinical trials in patients with compensated cirrhosis or mild liver impairment (Child-Pugh A) have shown that these medicines are well tolerated and highly effective. These medicines reduce the amount of HCV in the body by preventing it from multiplying, which over time leads to clearing the virus from the body, or HCV cure, which can prevent or limit liver damage from HCV. HCV is a contagious disease, and without treatment it can lead to serious liver problems, including cirrhosis, liver cancer, and death. When prescribed as indicated, these medicines continue to be safe and effective.

Health care professionals should continue to prescribe Mavyret, Zepatier, or Vosevi as indicated in the prescribing information for patients without liver impairment or with mild liver impairment (Child-Pugh A). Assess severity of liver disease at baseline and closely monitor for signs and symptoms of worsening liver function such as increases in liver enzymes, jaundice, ascites, encephalopathy, and variceal hemorrhage. Assessment of baseline liver disease and

close monitoring are especially important in those with pre-existing significant liver problems or risk factors, such as hepatocellular carcinoma or alcohol abuse, which can also contribute to clinical worsening of liver function or liver failure during treatment. Discontinue these medicines in patients who develop signs and symptoms of liver decompensation or as clinically indicated. Mavyret and Zepatier should not be prescribed in patients with any history of prior hepatic decompensation. Vosevi is indicated for patients who have previously failed certain other HCV treatments and is not recommended in patients with any history of hepatic decompensation unless the benefits outweigh the risk of liver injury, liver failure or death.

Patients should be aware that the risk of serious liver injury is rare. However, you should contact your health care professional right away if you develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools as these may be signs of liver injury. If you have liver impairment or other pre-existing risk factors that can worsen liver function such as a history of alcohol abuse, you should talk with your health care professional about the benefits and risks of the medicine. Do not stop taking these medicines without first talking with your health care professionals because stopping treatment early can lead to inadequate treatment, which could allow your HCV to come back. Over time, this could result in progression to severe liver disease and its complications, including cirrhosis, liver cancer, and death. These medicines have been widely used and are safe and effective in patients without liver impairment or in those with mild liver impairment for whom they are indicated.

We identified 63* cases of worsening liver function called liver decompensation with regimens Mavyret, Zepatier, and Vosevi to treat hepatitis C. Some of these cases led to liver failure and death. Most of these patients had moderate to severe liver impairment and should not have been prescribed these medicines. This number includes only cases submitted to FDA* or those found in the medical literature, so there may be additional cases about which we are unaware (see Data Summary). In 2018, an estimated 72,000 patients received dispensed prescriptions for Mavyret, Zepatier, or Vosevi from U.S. outpatient retail and mail-order/specialty pharmacies.

To help FDA track safety issues with medicines, report side effects involving Mavyret, Zepatier, Vosevi, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS).

Facts about Mavyret, Zepatier, and Vosevi

- Mavyret and Zepatier are treatment options for patients without liver impairment or those with mild liver impairment (Child-Pugh A).
- Mavyret is FDA-approved for use in adult and pediatric patients 12 years and older or weighing at least 45 kg with chronic hepatitis C virus (HCV) genotype 1,2,3,4,5, or 6 infection without liver impairment or with mild liver impairment (Child-Pugh A). It is a fixed-dose combination of glecaprevir and pibrentasvir.
- Zepatier is FDA-approved for use in adult patients with chronic HCV genotype 1 or 4 infection without liver impairment or with mild liver impairment (Child-Pugh A). It is a fixed-dose combination of elbasvir and grazoprevir.

- Vosevi is FDA-approved for use in adult patients with chronic HCV infection without liver impairment or with mild liver impairment (Child-Pugh A) who have:
    - Genotype 1,2,3,4,5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor
    - Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor

  It is a fixed-dose combination of sofosbuvir, velpatasvir, and voxilaprevir.
- These medicines are available as tablets taken by mouth. They reduce the amount of HCV in the body by preventing it from multiplying and over time leads to clearing the virus from the body, or HCV cure, which can prevent or limit liver damage from HCV.
- Common side effects include headache and tiredness.
- In 2018, an estimated 72,000 patients received dispensed prescriptions for Mavyret, Zepatier, or Vosevi from U.S. outpatient retail and mail-order/specialty pharmacies. Of these, 89% received a dispensed prescription for Mavyret, 6% received Vosevi, and 5% received Zepatier.[1]

Additional Information for Patients and Caregivers

- FDA has received reports that the use of Mavyret, Zepatier, or Vosevi to treat chronic hepatitis C in patients with moderate to severe liver impairment (decompensated liver cirrhosis, Child-Pugh B or C) has resulted in rare cases of life-threatening decompensation of liver function or failure and death. Some of these patients had other risk factors known to cause liver injury such as alcohol abuse. In most patients, symptoms resolved or new onset worsening of liver function improved after stopping the medicine.
- These medicines are not indicated for use in patients with moderate to severe liver impairment. These medicines have been widely used and are safe and effective in patients without liver impairment (no cirrhosis) or with mild liver impairment (compensated cirrhosis, Child-Pugh A).
- Do not stop taking these medicines without first talking to your health care professional. Stopping treatment early can lead to inadequate treatment, which could allow your hepatitis C virus to come back. Over time, this could result in progression to severe liver disease and its complications, including cirrhosis, liver cancer, and death. Contact your health care professional right away if you experience any of these signs and symptoms of liver problems while taking these medicines:
    - Fatigue
    - Weakness
    - Loss of appetite
    - Nausea and vomiting
    - Yellow eyes or skin
    - Light-colored stools
- Read the patient information leaflet when you receive a prescription for Mavyret, Zepatier, or Vosevi because there may be new or important additional information about your medicine. The leaflet explains the important things you need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.

- To help FDA track safety issues with medicines, report side effects from Mavyret, Zepatier, Vosevi, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA has received reports that the use of Mavyret, Zepatier, or Vosevi to treat chronic hepatitis C in patients with moderate to severe liver impairment (Child-Pugh B or C) has resulted in rare cases of life-threatening decompensation of liver function or liver failure. These events typically occurred within the first 4 weeks of starting treatment. Most patients had resolution of symptoms or liver function improvement after stopping the medicine, but some died.
- These medicines are not indicated for use in patients with moderate to severe liver impairment. These medicines have been widely used and are safe and effective in patients without liver impairment or in those with mild liver impairment (Child-Pugh A), for whom they are indicated.
- In many of the reported cases, liver failure occurred in patients who had signs and symptoms of advanced liver disease or other serious liver problems and should not have been treated with these medicines. In some cases, patients were reported as having no liver impairment or mild liver impairment (Child-Pugh A) at baseline despite having evidence of a previous decompensation event, portal hypertension or decreased platelets at baseline. In addition, some cases had other significant pre-existing risk factors such as hepatocellular carcinoma, alcohol abuse, or serious medical illnesses associated with serious liver problems.
- Perform hepatic laboratory testing as clinically indicated.
- Monitor for clinical signs and symptoms of hepatic decompensation such as the presence of jaundice, ascites, hepatic encephalopathy, and variceal hemorrhage.
- Discontinue Mavyret, Zepatier, and Vosevi in patients who develop evidence of hepatic decompensation or as clinically indicated.
- Encourage patients to read the prescribing information leaflet they receive with their Mavyret, Zepatier, or Vosevi prescriptions because there may be new or important additional information about the medicine.
- To help FDA track safety issues with medicines, report adverse events involving Mavyret, Zepatier, Vosevi, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.
- Other effective FDA approved treatment options are available for patients with cirrhosis who have moderate to severe liver impairment (Child-Pugh B or C).

Data Summary

FDA identified 63 cases of liver decompensation, including liver failure and death, associated with the use of hepatitis C medicines Mavyret (n=46), Zepatier (n=14), and Vosevi (n=3) reported in the FDA Adverse Event Reporting System (FAERS) database and in the medical literature through January 8, 2019. Ten cases reported isolated hyperbilirubinemia and jaundice without concomitant evidence of increased transaminase levels or other hepatic decompensation events, and eight cases reported deaths.

Of the 63 cases, 13 were in patients without cirrhosis, 18 with compensated cirrhosis, 21 with decompensated cirrhosis, and 11 with unknown liver function status at baseline. More than half of the cases that reported no cirrhosis or compensated cirrhosis (Child-Pugh A) at baseline were incorrectly classified and had evidence of advanced liver disease or pre-existing risk factors such as decreased platelets at baseline, portal hypertension, and alcohol abuse, or other serious medical illnesses impacting the liver prior to receiving treatment that may have signified or directly contributed to the development of hepatic decompensation or liver failure.

The median time to onset of a liver-related event or liver decompensation after initiating treatment was 22 days, ranging from 2 days to 16 weeks. The most frequently reported liver-related events were hyperbilirubinemia (n=42), jaundice (n=32), ascites (n=27), and hepatic encephalopathy (n=12). Discontinuation of the drug resulted in resolution of symptoms or reduced liver biochemical values in 39 of the 63 cases, and there were two cases of recurrence of symptoms upon re-initiating treatment.

References

1. Symphony Health PHAST Patient Monthly. 2016-2018. Data extracted Jan 2019.

Related Information

- Hepatitis C
- The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective
- Think It Through: Managing the Benefits and Risks of Medicines